UTILITY PATENT APPLICATION

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for

Hydrazide substrate safely shuts down disease activated protease to halt viral replication, cancerous cell division, and toxic protein generation

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefits of Provisional Application 60/459,694, filed April 2, 2003.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

(Not Applicable)

BACKGROUND OF THE INVENTION

[0001] Field of the invention

[0002] This invention relates in general to the hydrazide type protease inhibitors used to shutdown ongoing protein biosynthesis in cells, and more particularly as it relates to the mono amine oxidase inhibitor (MAOI) pharmaceuticals that shuts down ongoing protein biosynthesis irreversibly as a method used to inhibit oxidase for antidepressant drug purposes, and most particularly this invention uses the MAOI hydrazide inhibitor method to target and shutdown cells with ongoing protein biosynthesis of metastatic and disease related proteins for purposes to target and eradicate diseased cell as those which host cancer and viral infections.

[0003] General idea of the claimed invention

[0004] The general idea of the present invention is to use the existing MAOI hydrazide targeting mechanism that functions to target and shutdown ongoing protein biosynthesis in cells that

provides a means to inhibit oxidase biosynthesis provided by active CNS cells so as to increase mental stimulation as an antidepressant method. The same MAOI hydrazide mechanism provides a novel new purpose to target and shutdown ongoing protein biosynthesis in cells that are active in metastatic and disease related protein biosynthesis that mainly include cancer and viral infections. The process of using MAOI hydrazides for disease eradication purposes is essentially the same as that used for antidepressant purposes. In essence the process of targeting ongoing protein biosynthesis as exists for metastatic proteins as used for purging, and replacing cells that host cancer, viral infection, or related maladies is the same as that which already exists for MAOI use that targets and shuts down cells producing oxidase for antidepressant purposes.

[0005] Information known to the applicant

[0006] The MAOI hydrazide drugs appeared in the 1950's as a very effective way to treat mental depression. The mechanism was determined to be due to an oxidase inhibitor mechanism which allowed for an increase of CNS biogenic amine levels to occur that stimulated the CNS. The MAOI hydrazide action was determined to be due to an "irreversible substrate" mechanism which produced the antidepressant effects that followed protease cleavage of the hydrazide substrate which lasted for several weeks after the drug tenure ceased, Cutting's Handbook of Pharmacology, 6th ed., p. 628-629, 1979. The irreversible substrate mechanism thus shutdown protease in cells having ongoing protein biosynthesis activity to provide a permanent protein biosynthesis dysfunction that inhibited oxidase to provide the antidepressant effects but that also inhibited biosynthesis of replacement protease needed to reverse the disorder. As such the protein biosynthesis dysfunction can only be mediated by cell apoptosis and replacement. For this reason the MAOI antidepressant effects continued for several weeks following the tenure of the drug and essentially ends when the static cells undergo apoptotic breakup and is replaced with a new cell.

[0007] The applicant believes that the hydrazide molecular structure that provides the MAOI type irreversible substrate mechanism is essentially a molecule having no activity other than that provided by the prodrug mechanism which is manifested only in response to protease cleavage of the hydrazide substrate that releases the reactive hydrazine moiety. It is the active hydrazine that bonds irreversibly with the protease enzyme that causes its shutdown. Most of the prior art examples of the 1950's use such hydrazide irreversible substrate action which is exhibited by

molecules that are easily targeted by protease cleavage because there exists no molecular obstructions to block protease cleavage targeting, or that could attenuate such targeting activity. The type molecule structures that can provide the hydrazide MAOI mode of use generally have molecular weights between 150 and 300 that consist of an organic acid moiety condensed with an alkyl hydrazine moiety where the alkyl part is often extended further in a straight line manner. Such molecules have no activity other than the prodrug action provided by hydrazide cleavage. The MAOI prototype drug Iproniazid (Marsilid) has a therapeutic dose of 50-150 mg daily by mouth and has 1760 mg/kg lethal dose for mice as listed by Psychotropic Drugs and Related Compounds, Public Health Service Publications No.1589 (19867).

[0008] Information related to the present invention

[0009] In essence prior art inventors of the 1950's era used hydrazides to shutdown protein biosynthesis capability in cells using simple molecular constructions to provide various novel uses based on the irreversible substrate mechanism. The basic difference is that each novel use provides for a different purpose for such hydrazide method as does the present invention. Prior art inventors were not cognizant of the protein biosynthesis shutdown mechanism but nevertheless used such mechanism to provide uses for various different purposes which are all based on a common premise used by the present invention:

(a) That without a functioning protease enzyme the cell cannot synthesize viral coat protein for a viral infected cell;

(b) Without a functioning protease enzyme the cell cannot synthesize peptide signals that induce cancerous cell division, or that synthesize cancer metastatic proteins;

(c) Without a functioning protease enzyme the cell cannot produce toxic or aberrant protein products as is suspected to exist for some medical conditions where an aberrant protein product, a protein plaque, or other toxic protein product is being produced;

(d) Without a functioning protease enzyme microorganisms are rendered static and cannot produce bioactive peptide signals that induce cell division, and as such the organisms cannot divide, reproduce, grow, or proliferate;

(e) Without a functioning protease enzyme microorganisms cannot produce enzymes that detoxify or repair antibiotic damage and as such succumb more quickly to antibiotic action;
Prior art illustrates some such uses as follows:

[0010] Hydrazide halts peptides for plant growth inhibitor purposes

[0011] Malazide or maleic acid hydrazide was used by Schoene and Hoffman in 1949 as a plant growth inhibitor that was used as a spray to stop "suckering" or new plant growth in tobacco farming. Such chemical spray was applied before harvest time probably to increase nicotine content. Similar uses also exist where maleic hydrazide is presently used to prevent biological changes as budding, ripening, and to retard spoilage of farm produce. The biological mechanism is true to the irreversible substrate mechanism addressed above because the hydrazide substrate is targeted by plant cell protease cleavage which causes the dysfunctional shutdown of protease that renders such cells static and unable to produce protein or peptide signals that otherwise would induce biological changes. This result occurs because the hydrazide caused shutdown of protease cleavage halts cell biosynthesis of such peptides that otherwise would cause cell division, budding, ripening, and other natural processes to occur. As such the hydrazide provides use to extend the shelf life of farm produce and to inhibit new growth of plants. Such method has shown a history of safe use for tobacco and grocery produce items consumed by the public. Malazide was patented by U.S. Rubber Co., U. S. Patent 2,575,954,1951.

[0012] Hydrazide halts peptides for tuberculostatic purposes

[0013] Isoniazid or Isonicotinic acid hydrazide (U. S. Patent 2,830,994,1958 to Distillers Co.), was used by Fox in 1952, as a tuberculostatic agent, Cutting's Handbook of Pharm. 6th ed., p. 40, 1979. In effect Fox discovered that this chemical functioned as a tuberculostatic agent that far exceeded all other substances screened. Isoniazid was not of an inert alkyl-hydrazide design that provides a prodrug mechanism like the preferred embodiment of the present invention, but had an exposed hydrazine terminal having a reactive hydrazine characteristic that caused neurotoxic effects and other metabolic dysfunctions. This negative effect was attributed to hydrazine because without an alkyl or other blocking group it easily combined with chemical functional groups found in serum. It combines most easily with ester groups, ketones, and amides and as such is transformed in vivo to various compounds. However the antimicrobial effect sought after would need to be detrimental to the tuberculosis organism and to some extent that was provided by Isoniazid at the comparatively very high dose levels required which was more injurious to the microorganism than to the patient.

[0014] The Isoniazid molecule was noted by Fox as being deactivated mostly by systemic acetylation that would have provided a useful hydrazide effect was it not for the drug's hydrophilic nature and the rapid excretion found in about half the patients treated with Isoniazid. The applicant believes that this metabolic pathway predominated because the reactive hydrazine terminal was exposed in vivo to react with plasma constituents because it did not have an alkyl or other substituent that would have blocked its conjugation with plasma constituents. Fox later tried the nontoxic alkylated form of this product that negated the untoward toxic effects. That new product was labeled Iproniazid, but Iproniazid did not harm the multicellular tuberculosis organism or hasten its demise sufficiently which made Isoniazid the preferred choice as a tuberculostatic agent.

[0015] Hydrazide halts oxidase protein for antidepressant purposes

[0016] Iproniazid or Isonicotinic acid 2-isopropylhydrazide, was researched in 1952, by Zeller following Fox's report that it raised the mood of patients given the drug during his testing on tuberculosis patients, Cutting's Handbook of Pharm. 6th ed., p.125; 1979. The research indicated that Iproniazid was active as a mono amine oxidase inhibitor, or MAOI, which explained the euphoria and positive spirits exhibited by the patients receiving the drug. As a result Iproniazid was soon afterward produced as an antidepressant drug and the overwhelming therapeutic success motivated the development of Isocarboxazid, and Nialamide, as well as a number of MAOI hydrazide drugs never produced commercially .

[0017] The hydrazide type mono amine oxidase inhibitor (MAOI) provides an irreversible hydrazide substrate type action. Such irreversible substrate is due to hydrazide shutdown of protease irreversibly as a method used to stop ongoing protein biosynthesis which inhibits oxidase protein production. The oxidase enzyme has a function to degrade biogenic amines, or neural stimulants, as norepinephrine, noradrenaline, and as serotonin provides examples. The optimal levels are provided by a biological regulation scheme that increases biosynthesis of oxidase enzymes as needed to oxidize or deactivate levels of biogenic amines. The applicant believes that the biogenic amine degradation occurs only where the oxidase enzyme introduces oxygen to the alpha-carbon of the biogenic amine stimulant molecules to form an amide function which has no stimulation effects, whereas the hydrazide shutdown of oxidase biosynthesis prevents oxidase and hence oxidase degradation which allows biogenic stimulates levels to increase.

[0018] Hydrazide halts metastatic proteins for antiviral purposes

[0019] In about 1953, Thompson discovered antiviral action provided by a thiosemicarbazone derivative, Methisazone or 1-Methylindole-2,3,-dione 3 thiosemicarbazone, Cutting's Handbook of Pharm. 6th ed., p.125. Such hydrazide compounds proved very effective against smallpox, polio, and other viruses screened which became a commercial product known as Marboran. The applicant believes that Thompson had discovered the antiviral action existing in a hydrazide laboratory reagent compound which at relatively high dose levels was able to provide antiviral use that shutdown protease cleavage action. Unfortunately his hydrazide antiviral discovery was packaged in a molecule structure that was poorly suited for pharmaceutical uses. The applicant believes that Thompson had made a serendipitous discovery using a semicarbazone laboratory reagent used to separate ketones and aldehydes from solution which explains the very hydrophilic nature of the molecule used by Thompson which required a comparatively large dose necessary to get enough drug to the protease cleavage site to halt viral replication and shutdown the viral infected cells. Such comparatively huge dose level also provided undue side effects. The literature proposes that his antiviral discovery worked because it caused a defect in protein incorporation into the virus particle due to absence of attachment of mRNA to the ribosome. The applicant agrees with such explanation in respect that following the hydrazide shutdown of protease there is indeed a cell dysfunction that prevents protein biosynthesis illustrated by the absence of attachment of mRNA to the ribosome.

[0020] The applicant believes that the additional molecular structure that Thompson thought necessary to target the virus particle was misleading and was similar to the hybrid protease selective molecules of the 1990's in respect to molecule attributes that attenuate the hydrazide prodrug mechanism so that molecular properties can predominate to provide molecule affinity to select a particular protease enzyme targeted for inhibition. In Thompson's case such attenuated hydrazide type effect required larger dose levels, and as such the use of the antiviral agent was accompanied by nausea and vomiting. The level of hydrazide molecules useful to shutdown cell protease based on the classic MAOI model of Iproniazid, is a dose level of 50 mg, where as with the molecular additions and hydrophilic nature of the molecule used by Thompson with Marboran, a dose level of 1500 to 3000 mg daily were necessary to shutdown the viral infections. The applicant believes that had Thompson discovered that it was the hydrazide function that made his

antiviral molecule work he could have used the simple and more lipid soluble MAOI hydrazide product provided by Iproniazid to provide the needed efficacy without the side effects which would have provided for the rapid shutdown of all viruses at a 50 mg daily dose level.

[0021] Hydrazide halts degradation enzymes for homogenate preservation purposes

[0022] Iproniazid or Isonicotinic acid 2-isopropylhydrazide supplied by Aldrich Chemical Co., Milwaukee, Wisconsin; further illustrates the shutdown of cell protein biosynthesis capability illustrated by the MAOI hydrazide drug Iproniazid, supplied for another new purpose used to preserve tissue homogenates. For this type purpose Iproniazid, the classic MAOI hydrazide drug prototype, is added to the homogenate medium to prevent metabolic degradation or putrefaction of the homogenate. The hydrazide substrate provided by Iproniazide shuts down protease irreversibly such that live cells are rendered static and unable to divide, and biosynthesis of enzymes are inhibited that would otherwise provide digestive, oxidative, and other types of metabolic degradation of the homogenate. As such metabolic change and breakdown of the homogenate is prevented and bacterial contamination is inhibited from attacking the homogenate.

[0023] Cathepsin K hydrazides inhibit protease but not protein biosynthesis in cells

[0024] The prior art hydrazide discoveries of the 1950's era were simple pro drug molecules with the exception of the apparent serendipitous discovery that provided Marboran, the antiviral hydrazide. Then about 1990 a different type hydrazide appeared having hybrid molecular structures that provides selective protease inhibitor functions. Such class of compounds negate the prodrug action found in the simple hydrazide molecules of the 1950's era by nature of their complex hybrid molecular structures that provides action that targets the selected protease enzyme so as to window the hydrazide cleavage targeting action to the particular type protease enzyme molecule it inhibits. Such mechanism is exhibited by the present example used to inhibit cathepsin K enzymes disclosed by WO 97/16433, WO 98/48799, and WO 99/66925. The WO 97/16433, document on page 6 indicates that a structurally diverse variety of cathepsin K inhibitors already exist but are beset with metabolic side effects too severe for medical uses due to cytotoxicity, poor solubility, and other actions that cause over rapid plasma clearance. As such the subsequent patents disclose efforts to undertake the organic synthesis and evaluation of a myriad of different molecules types because some may provide, "selective inhibition of cathepsin K that may provide

an effective treatment for diseases of excessive bone loss," as stated on page 3 of WO 97/16433. Such types of products do not function to shutdown protein biosynthesis in cells and are unrelated in function and purpose to the present invention as explained in paragraph 34.

BRIEF SUMMARY OF THE INVENTION

[0025] General idea behind the claimed invention

[0026] The general idea behind this invention began with curiosity raised by an entry in the Merck Index, pertaining to Malazide, or maleic hydrazide, that stated that maleic hydrazide was used to stop the growth of tobacco plants which caused no harm to the plants. Such claim provoked questions as to what biological mechanism existed that could benignly stop cell division and growth and could such mechanism be adapted to stop cancerous cell division and growth for mammalian use. Based on the premise that cell division is triggered by, or is induced by peptide signals, then the inhibition of cell division must also be related to an inhibitor of protein biosynthesis provided by the maleic hydrazide molecule.

[0027] The similarity between a hydrazide molecular bond (R'NHNHCOR") and the amide bond (R'NHCOR") that links a peptide chain was readily noticed which indicated to this applicant that hydrazides are protease inhibitors that shuts down protein biosynthesis by providing a hydrazide substrate that becomes targeted by protease cleavage. Accordingly an irreversible protease shutdown mechanism was recognized to exist that did in fact shutdown ongoing cell protein biosynthesis capability, and that the more incessant such protein productions are, as exists with cancer metastatic and viral coat protein production, then the more quickly and likely hydrazide cleavage occurs early on to halt protein biosynthesis capability. As such the general idea behind this invention was realized as providing a remedial treatment for DNA resident diseases, most notably cancer and viral infections, but that also provides a method applicable to many maladies related to abnormal protein products caused by damaged or diseased altered DNA.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING

(Not applicable)

DETAILED DESCRIPTION OF THE INVENTION

[0028] Process of making the invention

[0029] This invention uses the hydrazide type mono amine oxidase inhibitor type antidepressant class of pharmaceuticals to provide a disease targeting and eradication purpose which does not require the chemical synthesis of a new compound before the invention can be used.

[0030] The new purpose invented

[0031] This present invention uses hydrazides to shutdown and disable ongoing protein biosynthesis irreversibly in cells that are actively producing metastatic and other abnormal protein products to achieve a disease eradication purpose. The prior art section has listed 7 working examples of hydrazides used to shutdown protein biosynthesis capability in cells for various purposes as summarized in paragraphs 64 and 65. Iproniazid, the MAOI hydrazide substrate drug that provides the preferred embodiment of the present invention illustrates three of the working examples provided by the shutdown of protein biosynthesis capability: (1) Iproniazid was first used for the purposes to inhibit tuberculosis proliferation and growth by inhibiting peptides that induce cell division and growth, but such use did not hasten the demise of the bacillus and was replaced with Isoniazid as a preferred tuberculostatic drug. (2) Iproniazid was next used for purposes to inhibit protein biosynthesis in cells producing oxidase that increased mental stimulation and feeling of well being. (3) Iproniazid was later used for purposes to preserve tissue homogenates by inhibit peptides that provided cell division and enzyme biosynthesis used to metabolize and putrefy the tissue homogenate medium and prevented bacterial action. (4) And herewith the present invention uses Iproniazid for a fourth new purpose to shutdown cells producing metastatic and disease related proteins by cells that host cancer and viral infections.

[0032] Distinguishing this invention from others

[0033] Although the previous uses of hydrazides are based on the shutdown of protein biosynthesis, no previous use of hydrazide has existed for purposes to target and shutdown cells that host cancer, viral disease, or abnormal protein products as the present invention provides. However Marboran, which uses semicarbazone, a molecule like that used as a laboratory chemical reagent was used by Thompson in 1953 to shutdown smallpox and polio viral infections. Such

apparent serendipitous discovery was not based on a molecule design having the needed pharmaceutical properties but was in fact a molecule hahydrophilic and toxic chemical reagent. As such Marboran did not have a prodrug molecule free of side effects and consequently Marboran provided cytotoxic effects. The use of the semicarbazone molecule required 1500 to 3000 mg daily dosage to provide the same prodrug antiviral effects that Iproniazid is estimated to provide at 50 to 100 mg. The cytotoxic proteins are also prevented in hydrazides that operate in the prodrug or MAOI mode because such mechanism involves the complete shutdown of protein biosynthesis capability for the cell and as such the cell is unable to produce any cytotoxic or other fragmented protein products.

[0034] There are essentially two principal types of hydrazide protease inhibitors, the type used by the present invention that functions to shutdown ongoing protein biosynthesis in cells, and the type used by the selective protease inhibitor that functions to inhibit a specific protease enzyme action for purpose to prevent a specific protein metabolism action from occurring. The cathepsin K selective protease inhibitors addressed by WO 97/16433, 98/48799, and 99/66925 provides such examples. The enzyme selective protease inhibitor provided by cathepsin K provides use to inhibit in a "reversible substrate" fashion the cathepsin K protease. Cathepsin K has a systemic use to metabolize a protein product that mediates a bone loss process while the bone is in a state of flux being disassembled and reassembled as occurs with normal bone growth. The purpose of the cathepsin K inhibitor seems to be to block the bone disassembly side of the process while the rebuilding phase continues thus providing a purpose to stop bone loss. Such cathepsin K and other hydrazides that have a protease enzyme selective feature are unrelated to the MAOI hydrazide by type mechanism, method, use, and purpose.

[0035] MAOI mode of use and mechanism

[0036] The existing mono amine oxidase inhibitor (MAOI) hydrazide drugs provide a long history of antidepressant type use that began about 1953. The applicant believes it provides an antidepressant action because CNS activity releases biogenic amine stimulants which increase mental activity in the cells immediately in use. The stimulant action must then be negated after the thought process moves further on to new cells. As such the CNS cells involved begin synthesizing oxidase enzymes that provides the metabolic degradation action required to degrade the biogenic

stimulants into a non stimulating amide metabolite. The degradation process provided by oxidase is halted by the MAOI hydrazide drug because it provides a hydrazide substrate that is targeted by protease cleavage that shuts down protein biosynthesis capability in the active cells. Such process inhibits oxidase protein biosynthesis but nevertheless allows the cells to remain mentally or electrically active in the stimulated state long after the tenure of the MAOI drug ends. Such cells cannot repair its protein biosynthesis dysfunction although they may remain as viable CNS cells until cell apoptosis occurs and the cells are replaced.

[0037] The present invention uses this MAOI drug mechanism for a new purpose to target and shutdown cells that host cancer, viral, and other diseases that provides abnormal protein products. The action accordingly provides a new use and purpose for MAOI hydrazide drugs to shutdown ongoing protein biosynthesis of cells that host diseases which essentially functions by shutting down the most active protein producing cells first and the least active last. As such a targeting mechanism exists that is based on the amount of protease cleavage or cell biosynthesis activity that is ongoing because it is the targeting of the hydrazide substrate during the protein biosynthesis process that shuts down biosynthesis capability that induces cell apoptosis and replacement. Therefore cells hosting an aggressive cancer or viral diseases that is incessantly involved in protein biosynthesis necessary to supply protein for cell division and metastasis processes are the primary targets by the process. A cell that is not involved in protein biosynthesis cannot be shutdown by the process and are unaffected. However non diseased cells involved in protein biosynthesis as exists occurs with CNS cells that produce oxidase are shutdown, however such is a benign process because the cells are also replaced with a disease free cell replacement.

[0038] Hydrazide biological mechanism

[0039] This present invention is based on the biological mechanism unwittingly used numerous times by prior art process that served various purposes as listed in paragraphs 10 through 22. The hydrazide molecule simulates the substrate material used in the protein biosynthesis operation, and when protein biosynthesis is ongoing and a hydrazide substrate becomes targeted by protease cleavage action instead of the usual substrate material where the acid to hydrazine bond is broken which releases the reactive hydrazine moiety that in turn bonds to the protease molecule thus obstructing protease action and hence shuts down protein biosynthesis activity. The targeting of

the hydrazide substrate by cell protease occurs naturally because the hydrazide substrate contains an amide type bond (R'NHCOR") which also exists in a hydrazine to acid bond (R'NHNHCOR") that simulates the links of the amino acids chains. Such action obstructs enzyme cleavage thereafter and renders the cell dysfunctional.

[0040] Such action effectively shuts down cell protein biosynthesis irreversibly because a replacement protease cannot be synthesized without a functioning protease enzyme needed to participate in such biosynthesis action. Such impasse renders the cell static and unable to synthesize protein products required for normal cell operation or maintenance. Consequently the static cell condition can only last until the cell environment deteriorates to a point where cell apoptosis is triggered thus allowing for a replacement cell to be provided. In this way the intentional shutdown of protein producing cells as that hosting disease mechanisms can be provided using the MAOI hydrazide drug method because it provides a means to target and shutdown the most active protein producing cells first, and especially those having incessant recursive DNA disease algorithms as exists for cancer, and viral diseases. Such diseased cells thus become the preferred and primary targets for hydrazide shutdown action due to incessantly disease activity that produces a continuous stream of metastatic, antigenic, abnormal, and other disease related protein products. The applicant believes that cells which produce abnormal cell proteins are always indicative of cancer, viral infections, and similar DNA disease algorithms or damage done to the DNA, and that the more prolific the abnormal protein production is then the more rapidly such cells become shutdown as would occur early on during hydrazide therapy. And within about a three week window that follows cell shutdown the cells are rendered static and succumb to apoptosis and replacement with disease free cells.

[0041] Information needed to safely use MAOI hydrazides

[0042] This invention uses the existing MAOI hydrazide drugs of the 1950's era for a new purpose that targets and shuts down cells that host cancer, viral disease, and related maladies. Irregardless of the severity or stage of the disease, the same dosage levels, drug interaction precautions, and treatment regimen required for MAOI antidepressant use also applies for disease eradication uses. The MAOI prototype drug Iproniazid (Marsilid) has a therapeutic dose of 50-150 mg daily by mouth and has 1760 mg/kg lethal dose for mice as listed by Psychotropic Drugs and Related

Compounds, Public Health Service Publications No.1589 (19867). The drug was introduced about 1952 and is still used in some countries abroad according to Drugs Available Abroad, Page 520, Derwent Publications Ltd., London England. The applicant believes that such prodrugs are not toxic per se, and are considered safe if the patient has not consumed toxic materials as exists with alcohol or drug abuse, or other drugs having a MAOI warning label. The contradicted drugs are addressed by Cutting's Handbook of Pharmacology, 6th ed., p. 628-629, 1979 which lists CNS depressants, narcotic analgesics, anticholinergics, and dibenzazepine antidepressant drugs. Hepatotoxicity should also be given consideration because the MAOI hydrazide will shutdown liver cells involved in the biosynthesis of enzymes required for detoxification which could cause problems for a patient addicted to alcohol or drugs if not clearly forewarned. And even though liver cells thus shutdown and recycled involves a benign process such can take up to three weeks before new cells are provided and full detox capability is restored. As such those skilled in the art should become aware of the MAOI drug's manufacturer's recommended dosage levels and contradicted substances before using MAOI products required by this invention.

[0043] Best mode contemplated to treat viral infections

[0044] Hydrazide rapidly halts viral infections because such diseases take control of host cell resources and begins protein biosynthesis of viral protein products such that a hydrazide substrate is soon targeted by protease cleavage which ends the viral infection. The applicant believes the RNA virus as provides HIV essentially begins with an infectious virion particle that has an affinity for the immune system t-cell surface where it becomes invaginated into the cell. There the RNA encoded sequence is translated by reverse transcription back into DNA which then takes control of cell resources and begins viral replication. The DNA program essentially provides a process that will loop in recursive fashion never to end the viral replication process. The process comprises the DNA algorithm for the assembly of the virus such that the DNA code is transcribed into RNA, and the RNA is translated into the protein equivalent. Protease cleavage that is necessary to supply the protein biosynthesis portion of such assembly will quickly target the hydrazide substrate to shut down the viral replicating process thus halting the protein phase of the operation that renders the cell static and doomed for apoptosis and cell replacement. Otherwise if no hydrazide substrate is present the mRNA action provides for the protein assembly that when complete while still attached to the RNA is pushed out of the host cell to find a new host cell and repeats the process.

[0045] In essence the hydrazide targeting method shuts down disease activated protease first in the cells most active in providing biosynthesis of viral coat protein and other disease related products. Such action ends the metastatic protein production and shuts down the viral infection whether the virus is the most virulent of all viruses or the most insignificant of all infections. The moment cell protein biosynthesis is shutdown by the hydrazide substrate action the cell is rendered static and sterile without disease activity where such static state induces apoptosis to occur within a three week window that follows. The HIV/AIDS virus is most vulnerable to hydrazide therapy because it's a large virus that requires much more time and proteolysis material to replicate, which increases the time and opportunity for the smallest dose levels of hydrazide to be targeted by protease cleavage before a complete virion packet can be produced. The best mode contemplated by the applicant to target and shutdown all viral replicating cells irregardless of the type of viral infection is to administer a pharmaceutical preparation of a MAOI hydrazide drug as Iproniazid provides example, at a dose level or less as MAOI antidepressant use would require until the viral load is zero or the disease is otherwise determined to be in full remission. Additionally Iproniazid exists in some laboratories used as a preservative for tissue homogenates and as such a laboratory source of Iproniazid may be used to illustrate the rapid antiviral mechanism using animal models.

[0046] Best mode contemplated to treat cancer

[0047] Cancerous growth, and its metastasis is quickly blocked by action of the hydrazide substrate drugs. This is because cells that host cancer are generally very active providing for the biosynthesis of numerous protein products required by cell division and necessary to produce the metastatic protein envelope that transports the RNA cancer algorithm in tact to its new host cell. The applicant believes the similarity between cancer and the RNA virus as addressed above is striking in respect that cancer and viruses are encoded into nucleic acid which redirects cell action to provide a metastatic protein packet. The difference being that the cancer DNA program provides an additional means to activate a cell division processes. As such the complete DNA cancer program code is replicated when encoded into RNA media and then translated into a matching protein sequence. And much like the viral model where such RNA is held together by its protein envelope, such RNA packet is pushed out of the cell intact by successive packets produced. As such the metastatic protein package holds together the RNA cancer algorithm medium where it becomes invaginated into a neighboring cell, and by reverse transcription

becomes installed in the new host's cells DNA. If the cancer is sufficiently malignant such metastatic packet could travel far to become invaginated into a new host cell located in other organs or tissue. Then by reverse transcription the cancer program sequence is again converted back to DNA and installed into the new host cell's DNA bundle as illustrated by the virus model. As occurs with the viral model the hydrazide substrate is rapidly targeted due to the incessant protein biosynthesis action that will immediately shutdown cancerous cell division and metastasis action irreversibly. The mode contemplated to purge cancer cells from the system is to administer a pharmaceutical preparation of an MAOI hydrazide drug at a dose level as MAOI use would require, until metastatic protein emissions cease and the disease is in full remission. MAOI type hydrazide testing on animal models could also be provided by Iproniazid to show independent verification of this claim as Iproniazid exists in many biology laboratories as a preservative for tissue homogenate.

[0048] Best mode contemplated to treat multiple myeloma

[0049] The applicant believes that multiple myeloma is based on a mechanism much like cancer that involves a sequence of DNA having the algorithm to provide bone and blood-related protein. The mechanism likely has a genesis based on damages that occur to the DNA protein sequence instructions portion of DNA such that the protein is assembled incompletely or defective. Such damage to the DNA that altered the DNA algorithm is probably due to free radical, radiation, or toxic substance type damages as occurs with age. Because such systemic need cannot be satisfied by the aberrant protein being produced by the damaged DNA code segment, the program it is held active to perpetually churn out the defective protein of a shorter unusable length, and as such would be somewhat characteristic of myeloma protein. And as somewhat exists with cancer, the corrupt DNA algorithm with each activation provided by a systemic need the altered DNA routine is transcribed into RNA media, which is then translated into protein that effectively provides a metastatic packet of the altered myeloma protein while it remains attached to the RNA counterpart. At which time the metastatic myeloma program packet would be pushed outside the cell by the successive reiterations of such operation ongoing in the cell. Such metastatic packet could then become invaginated into an adjacent cell. Such metastatic action then takes control of the neighboring cell whereby it becomes host to a cancer like mechanism that repeats the process where reverse transcription of the RNA reestablishes the mechanism into the new host cell.

[0050] The incessant disease activated protease system producing such aberrant myeloma protein products would easily be shutdown by the hydrazide substrate mechanism which would provide immediate relief and comfort to the patient without causing any untoward side effects. Secondly the disease would be placed in full remission very soon due to hydrazide substrate shutdown of the cells that host myeloma which follows with cell apoptosis and replacement with new cells provided by cell division of cells able to divide and not involved in the disease mechanism. Such myeloma remedial action could easily be verified using animal models based on the MAOI drug Iproniazid as used to preserve tissue homogenates. Many additional myeloma related disease applications are also possible for hydrazide drug therapy that becomes apparent based on findings that shows a disease mechanism responsible for providing abnormal proteins. Any abnormal protein must originate from the DNA encoded instructions such that an aberration of the protein product essentially mirrors an aberration that exists in the DNA counterpart. The mode contemplated to purge myeloma cells from the system is to administer a pharmaceutical preparation of an MAOI hydrazide drug at a dose level as MAOI antidepressant use would require or less until the aberrant protein emissions cease and the disease is in full remission.

[0051] Best mode contemplated to treat Alzheimer's disease

[0052] The applicant believes that all DNA resident diseases are characterized by abnormal protein products that are peculiar to the disease that essentially represents the disease altered sequence of DNA. In the case of Alzheimer's disease such peculiar protein plaque indicates a DNA code that is providing a transcribed code with an aberration from DNA to RNA which likewise appears in the protein translation. Such aberration may be due to spelling, folding, or length errors such that the protein is pushed outside the cells with its RNA compliment but where the RNA eventually detaches and the tough protein fiber remains to deposit as a plaque that accumulates around the CNS cell that produced it. The protein product that first spills outside the cell with the RNA attached to its protein component could provide metastatic action if it can become invaginated into adjacent cells before the RNA becomes separated. The interference and crowding of neurons by such plaque would eventually lead to atrophy of surrounding tissue causing dementia as is characteristic of the disease. However the biosynthesis of such aberrant protein product indicates protease enzyme activity which is subject to hydrazide therapy that would shutdown such diseased activity and the cells responsible. Because such dysfunctional cells

are unable to regulate their own environment when protease is shutdown such diseased cells would undergo apoptosis and the eradication of such Alzheimer diseased cells would result.

[0053] However the victim of Alzheimer's disease may hardly notice any change when a cure is provided as the atrophy and damage to surrounding tissue would remain for a while and the protein plaque deposit may need additional time and treatment to be removed before new neuron and dendrite growth can exist. As such the effects of the disease may remain sometime even though the mechanism producing the disease is eradicated. Full recovery could possibly be hastened using immune system adjuvants, a plaque vaccine, or like techniques. Additionally nerve growth stimulants would be useful to stimulate new nerve and dendrite growth that would hasten recovery of lost mental functions suffered by such victims. The best mode contemplated by this applicant to treat Alzheimer's disease is to administer a pharmaceutical preparation of an MAOI hydrazide drug at a dose level as MAOI use would require or less, and to continue such treatment until the symptoms disappear.

[0054] Best mode contemplated to treat biological regulation disorders

[0055] The applicant believes that the hydrazide substrate mechanism provides a use to purge cells that have damaged or altered DNA as results from free radical, radiation, or toxic substance type damages. Such DNA damage can accumulate in cells of a given tissue type or glandular function to negate or diminish the systemic need served by such organ. Such DNA damage is transcribed into RNA that is further translated into protein having an aberrant spelling sequence to negate that cell's ability to communicate biologically through such products as bioactive peptides, hormones, prostaglandin products, or like peptide molecules used to communicate biological action or need. Any corruption of that peptide product prevents such systemic communication processes from working because the peptide spelling and or allosteric properties would no longer match the intended complimentary allosteric receptor site that it must engage to activate the needed systemic response or actions that satisfy a needed response. Treatment to restore the proper address or combination sequence is possible in respect that the hydrazide drug mechanism is able to shutdown protease and force replacement of the DNA damaged cell with a new cell free of such DNA damage and accordingly such replacement would have the correct spelling and allosteric characteristics.

[0056] Such DNA damages accumulate with age and this applicant believes that such accumulated damage is the cause of many age related maladies. Diabetes provides an illustrative example based on the applicant's theory where a general diminishing of insulin levels is seen with age as may be caused by free radical, radiation, or toxic substance type damages to DNA. Such damage could begin where a single error becomes encoded into the long spelling sequence of the insulin molecule which would negate the insulin action. Such peptide template damage would require more and more insulin producing cells to remain active longer to produce enough viable insulin product to satisfy systemic needs. In effect the applicant believes that such diminishing effectiveness of the biological regulation process is due to such accumulated damages to the DNA nucleotide. The insulin molecule damage scenario is only one of very many possibilities that exists where corruption of the allosteric properties negates the intended effects of bioactive peptides, hormones, prostaglandin products, and essentially any protein or peptide product that exists.

[0057] The applicant believes the effects of such aberrant bioactive peptide products could be manifested in a numerous diversity of symptoms and conditions represented in a small part as allergic, metabolic, endocrine, neurologic, arthritic, some obesity, some schizophrenia, some autoimmune, anorexia, colitis, altered sensitivity to pain, some hypertension, psoriasis, cravings, addictions, eating disorders, and countless additional possibilities that could easily be determined based on positive results that would occur after a trial period of hydrazide substrate therapy. Use over a lengthy period of time such treatment would gradually purge and replace such aberrant or abnormal protein producing cells with new cells having full DNA integrity that are disease and damage free. The speed at which such age related malady could be reversed would correspond to how frequently the cell is called on to produce its protein product. The incessantly active cells providing protein biosynthesis would be immediately purged using the hydrazide method whereas the less active cells that are seldom involved in protein biosynthesis would take a lengthy period of treatment. The mode contemplated to purge such DNA damaged or abnormal protein producing cells from the system is to administer a pharmaceutical preparation of an MAOI hydrazide drug at a dose level as MAOI use would require, or less, over an extended period of time or until the associated symptoms have disappeared or when no further improvement is recognized to occur.

[0058] Best mode contemplated for prophylaxis use

[0059] Protection against disease is a need that exists concurrent with some conditions and following some treatment regimens which weakens the immune system response to infection and as such presents a problem that can be satisfied by using a hydrazide type protease inhibitor as a prophylaxes drug. Such need for protection against diseases also exists following exposure to infectious disease, radiation, stress, old age, or merely as a safeguard when infectious disease exposure is threatened. The principal hydrazide substrate drug used in this applicant's research was Iproniazid which has been used as an antidepressant drug for over 50 years in some countries abroad. And because the hydrazide type MAOI drug is essentially side effect free when MAOI drug interaction precautions are observed, and because there exists no tolerance or untoward side effects to preclude such continuous use, a small dose level at a quarter of that of that of the manufacture's recommended dose for antidepressant use should suffice to shutdown an infected cell quickly before such virus, cancer, or other maladies can develop symptoms, or the infection can spread systemically, or be communicated to others. Such prophylactic use could reasonably continue through life to protect one against most diseases and age related conditions or like maladies to provide a better quality of long life that would be virtually disease free.

[0060] Best mode contemplated as antibiotic adjuvant use

[0061] The hydrazide drug prevents peptide productions that induce cell division, growth, reproduction or proliferation of infectious organisms as bacterial, fungal, protozoal, metazoa, and such like. Although drug delivery to the organism is required, such is not a problem for systemic infections and as such are easily treated. The method suggested is essentially the same as the prior art examples that used Iproniazid to stop tuberculosis cell division or growth, and etc. In such examples the hydrazide substrate shuts down protein biosynthesis innately to the organisms that prevents cell division and growth. As such hydrazide use provides a means to stop microorganism infectious activity and its proliferation, but does not have any rapid means to kill or eradicate such existing microorganisms when a hydrazide drug is used alone. However hydrazide use has an advantage to hold reproduction and proliferation of such infectious organisms in check while trying antibiotics with questionable efficacy. Secondly hydrazide provides an adjuvant use that provides antibiotic synergy by preventing protein biosynthesis of enzymes innate to the microorganism such that the organism cannot metabolize, detoxify, block, or repair damage done

by the antibiotic effects. And a third important use would be to insure that any secondary type infections do not develop such as fungal infections often do during the use of antibiotic treatment for bacterial infections.

[0062] Antibiotic resistant organisms have become a major problem due to world population levels that are increasingly dependent on a limited number of antibiotic drugs. Such problems are exacerbated by the unnecessary and frivolous use of antibiotics in the livestock industry. Such problems and abuses would be negated if a hydrazide drug was prescribed concurrent with antibiotic use to prevent the microorganism from acquiring and passing on antibiotic resistance traits to progeny or successive generations. Such benefits are possible if a hydrazide type MAOI compound was added to antibiotic preparations, or simply added in minimal amounts to animal feed as a prophylaxes drug. Such uses would prevent livestock losses due to disease and prevent disease resistant strains from evolving that could threaten human life such as the crown virus, bird flu, and other viral mutations are beginning to provide. As such hydrazide use would cost very little to prevent viral infections for the livestock industry and bacterial infection losses would be minimized and resistant strains of microorganism would be prevented from evolving. Secondly strains of viruses are evolving that threatens a catastrophic the loss of human life and that could shutdown the world economy as to the bird flu has a potential to do. Such safeguard could be provided by hydrazide prophylaxis use, and for any existing bacterial infections such use could be adjuvant to antibiotic use. The mode contemplated to negate such threats and or provide adjuvant use for antibiotic therapy is to administer a pharmaceutical preparation of an MAOI hydrazide type drug concurrent with antibiotic medications at a dose level determined to be the minimal amount sufficient to provide adjuvant support for the type antibiotic being used. Only antibiotic or related agents that have been screened or are known to be free of hepatotoxic mechanisms would be candidates for such adjuvant use applications.

[0063] Summary of working examples used for different purposes

[0064] The present invention uses a hydrazide mechanism that targets and shuts down ongoing protein biosynthesis to provide many different useful purposes as the seven working examples listed in prior art have shown. The first working example is Malazide introduced in 1949, as a plant growth inhibitor which shutdown ongoing cell protein biosynthesis for purposes to inhibit

peptides that induced cell division or growth. Then in 1952, Iproniazid was used to shutdown ongoing cell protein biosynthesis action for tuberculostatic purposes that inhibited peptides that induced cell division and growth of the bacilli. Because the bacilli were not quickly terminated Isoniazid later replaced Iproniazid for such purpose. Then about 1953, Iproniazid used such method for antidepressant drug purposes by shutting down ongoing protein biosynthesis as a means to inhibit oxidase proteins in CNS cells. And about that same time in 1953, Marboran supplied a hydrazide substrate that shutdown ongoing protein biosynthesis to stop smallpox and polio virus replication. Then some time later Aldrich Chemical Company began supplying Iproniazid which is used for a third new purpose as a preservative for tissue homogenates. Iproniazid used for this purpose shuts down protein biosynthesis provided by cells in a tissue homogenate to inhibit peptides that induce cell division, and that also inhibits enzymes from being produced that would serve to metabolize or putrefy the homogenate. Such long chain of evidence continues with the present invention which provides a fourth purpose for Iproniazid's use which is to shutdown metastatic and disease related proteins in cells that host cancer, viral infections, or related maladies.

[0065] The anticancer type mechanisms that provides action to shutdown peptides that cause cell division and growth is also evidenced by working examples based on Malazide, Isoniazid, and Iproniazid. The antiviral mechanism use to target and shuts down cells producing metastatic viral coat protein has also been evidenced by Marboran despite the cytotoxic side effects caused by the semicarbazide type hydrazide molecule used by Marboran. The level of predictability for use to shutdown ongoing protein biosynthesis capability in cells that provides one more purpose for such use to halt biosynthesis in cells that host cancer and viral infections is without question another viable application for the prodrug MAOI irreversible substrate mechanism. The applicant believes such different purpose provided by the use of MAOI hydrazide drugs will provide a safe, pleasant, and rapid acting remedial treatment for cancer, viral disease, and all diseases having related pathology.

[0066] Alternative embodiments

[0067] This invention provides a medical or biological tool that can be used to shutdown ongoing protein biosynthesis in cells that provides many additional medical applications not possible to

addressed herein, but will be recognized by those skilled in the art that have knowledgeable of protein related disease pathology. Additionally this invention provides a new and different purpose for the MAOI hydrazide antidepressant drugs. Such MAOI hydrazides are use as the preferred embodiment required by the present invention and such MAOI hydrazide pharmaceuticals has a long history of safe medical use when used in accordance with the manufacturer's instructions. However many hydrazide compounds that are not labeled as MAOI hydrazides exist that also function to duplicate the MAOI prodrug mechanisms and as such could be used for the same purposes provided by this present invention. Additionally such new hydrazide structures and compounds could use precursors as hydrazine, or altered forms of hydrazides as sulfonyl hydrazides, thiohydrazides, diacyl type hydrazides, and other modified forms that could easily provide the uses and purpose provided by the present invention. As such the present invention should not be restricted to the existing MAOI drug embodiments or be limited to the uses cited in the application as many variations are possible without departing from the spirit, or scope or uses provided by the present invention. Additionally the applicant has used theory and hypothetical examples to illustrate the best mode contemplated by the applicant to provide the level of direction and guidance required by 35 U.S.C. §112, and as such the present invention should not be bound or limited by theory or the accuracy thereof.